IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of)
)
ANDREW J. DANNENBERG.) Group Art Unit: 1617
)
Patent Application No. 09/554,604) Examiner: S. Wang
)
Filed: May 31, 2000)
)
For: CYCLOOXYGENASE-2 INHIBITION)

BRIEF ON APPEAL (Three copies)

Honorable Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Transmitted herewith is a Brief on Appeal in the above-identified application.

1. ( ) An Oral Hearing is requested.
2. ( ) An Oral Hearing is requested on _____.
3. ( ) An extension of time for filing the Brief on Appeal
   ( ) is hereby requested.
   ( ) was requested on _____.
4. (X)Small entity status is claimed.

The Appeal fee is calculated as follows:

	Large Entity	Small Entity	Amount
Brief on Appeal	$320.00	$160.00	$160.00
Request for Oral Hearing	280.00	140.00	
Request for Extension of Time for Filing Notice for Appeal			
( ) 1 month	110.00	55.00	
( ) 2 months	400.00	200.00	
( ) 3 months	920.00	460.00	
( ) 4 months	1,440.00	720.00	
( ) 5 months	1,960.00	980.00	
		TOTAL DUE $	160.00

5. ( ) No fee required.

6. (X)A check in the amount of $160.00 is enclosed.
(Check No.17135)

7. ( ) Please charge Deposit Account No. 10-1213 in the amount of $_____. A duplicate of this sheet is enclosed.

8. (X) The Commissioner is hereby authorized to charge payment of the following fees during the pendency of this application or credit any overpayment to Deposit Account No. 10-1213. A duplicate of this sheet is enclosed.

(X) Any patent application processing fees under 37 CFR 1.17.
(X) Any filing fees under 37 CFR 1.16. for presentation of extra claims.

Respectfully submitted,

Eric S. Spector
Reg. No. 22,495

Date: July 8, 2002

JONES, TULLAR & COOPER, P.C.
P.O. Box 2266 Eads Station
Arlington, VA 22202
703-415-1500

Case: CRF D-2165

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of)
)
ANDREW J. DANNENBERG.) Group Art Unit: 1617
)
Patent Application No. 09/554,604) Examiner: S. Wang
)
Filed: May 31, 2000)
)
For: CYCLOOXYGENASE-2 INHIBITION)

#19
AKO
7.25.02

BRIEF ON APPEAL
(In Triplicate)

Honorable Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This is a Brief on Appeal directed to appeal of the final rejection of March 15, 2002 as modified in advisory actions dated May 1, 2002, May 29, 2002 and June 21, 2002. A Notice of Appeal was filed on June 25, 2002.

Following is compliance with 37 C.F.R. § 1.192(c).

(1) REAL PARTY IN INTEREST – 37 C.F.R. § 1.192(c)(1)

The real party in interest is Cornell Research Foundation, Inc.

(2) RELATED APPEALS AND INTERFERENCES – 37 C.F.R. § 1.192(c)(2)

No related appeals or interferences are known to appellant, the appellant's legal representative, or the assignee.

(3) STATUS OF CLAIMS – 37 C.F.R. § 1.192(c)(3)

Claims 1-16 were in the application as filed. Claim 17 was added in the response of January 7, 2002.

A restriction requirement was rendered on August 14, 2001. The claims were apportioned to Group I (Claims 1-6), Group II (Claims 7-11) and Group III (Claims 12-16).

Group I (Claims 1-6) was elected. Added Claim 17 is in Group I.

Claims 12-16 were canceled in the response of January 7, 2002.

Claims 1, 2, 6 and 8 were canceled in the response of April 16, 2002.

Claims 3-5, 7, 9-11 and 17 remain in the case.

Claims 3-5 and 17 are the only claims rejected and are all appealed.

Claims 7 and 9-11 which remain in the case have been withdrawn from consideration as constituting claims of a non-elected group. However, Claims 7 and 9-11 have been maintained in the application because they are considered allowable if Claims 3-5 and 17 are found allowable.

The appealed claims (Claims 3-5 and 17) are set forth in Appendix A hereto.

The claims that stand withdrawn from consideration (Claims 7 and 9-11) are set forth in Appendix B hereto.

(4) STATUS OF AMENDMENTS – 37 C.F.R. § 1.192(c)(4)

Amendments made after final rejection were cancellation of Claims 1, 2, 6 and 8 and amendment of Claims 7, 9, 10, 11 and 17. These amendments were made in the response of April 16, 2002 and were entered for purposes of appeal by the Advisory Action of May 1, 2002. The only appealed claim amended subsequent to final rejection was Claim 17; as indicated above, this amendment was entered for purposes of appeal by the Advisory Action of May 1, 2002.

(5) SUMMARY OF INVENTION – 37 C.F.R. § 1.192(c)(5)

The claimed invention is directed to a method of treating a patient affected with a liver disease selected from the group consisting of chronic viral hepatitis B, chronic viral hepatitis C, alcoholic liver injury and nonalcoholic steatohepatitis. The method comprises administering to the patient a cyclooxygenase-2 inhibiting amount of a selective inhibitor of cyclooxygenase-2 (See the application as filed at page 3, lines 4-10).

The particular inhibitors of cyclooxygenase-2 recited in Claims 4 and 5 find basis in the application as filed at page 16, lines 27-30.

The inhibitors of cyclooxygenase-2 for Claim 17 find basis in the application as filed at page 18, lines 3-9.

(6) ISSUES – 37 C.F.R. § 1.192(c)(6)

Whether Claims 3-5 and 17 are unpatentable under 35 U.S.C. 103(a) over Gregory et al U.S. Patent No. 6,172,096 in further view of Talley et al U.S. Patent No. 5,643,933 when any *prima facie* case has been overcome by the submission by applicant of published evidence and when the contentions by the PTO in rebuttal rely on overgeneralization, hypothesis and indefinite statement and when the prior art does not indicate a reasonable expectation of success for the claimed method.

(7) GROUPING OF CLAIMS – 37 C.F.R. § 1.192(c)(7)

All the appealed claims, i.e., Claims 3-5 and 17, stand fall together, so far as the sole rejection is concerned.

(8) ARGUMENT – 37 C.F.R. § 1.192(c)(8)

The Rejection

Claims 3-5 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gregory et al U.S. 6,172,096, in further view of Talley et al U.S. Patent No. 5,643,933. The contentions of the PTO appear to be that Gregory et al and Talley et al teach that selective inhibitors of cyclooxygenase-2 are generally known for treating inflammatory disease and that Gregory et al teaches that selective inhibitors of cyclooxygenase-2 are known for treating liver disease and that chronic hepatitis involves inflammation of the liver and therefore it would be obvious to administer selective inhibitors of cyclooxygenase-2 to treat chronic hepatitis.

Limitations in the Rejected Claims Not Described in the Applied Prior Art

The applied prior art combination fails to disclose treatment of the diseases treated in the claims, namely chronic viral hepatitis B, chronic viral hepatitis C, alcoholic liver injury and nonalcoholic steatohepatitis.

Errors in the Rejection

(1) The position that selective inhibitors of cyclooxygenase-2 are generally known to be useful for treating inflammatory disease, is overstatement.

(2) The position that the applied art combination teaches that selective inhibitors of cyclooxygenase-2 are known for treating liver disease is overgeneralization and overstatement.

(3) The rejection ignores that a consideration the art as a whole leads away from the invention.

Selective Inhibitors of Cyclooxygenase-2 Are Not Generally
Known To Be Useful for Treating Inflammatory Disease

The appropriate question is whether selective inhibitors of cyclooxygenase-2 were known to be generally useful at the effective date herein for treating inflammatory disease. Two articles were submitted with the response of May 15, 2002 that show the opposite is the case, namely that at the effective date herein, selective inhibitors of cyclooxygenase-2 were known not to be generally useful for treating inflammatory disease. The articles are Reuter, B.K., et al, J. Clin. Invest. 98, No. 9, 2076-2085 (11/96) and Mizuno, H., et al, Gastroenterology 112, 387-397 (1997). Reuter et al concluded that their studies demonstrate that suppression of cyclooxygenase-2 can result in exacerbation of inflammation associated colonic injury (See Abstract). Mizuno et al concluded that its data shows that high levels of COX-2 mRNA and protein during the acute stages of gastric mucosal lesions may be involved in the repair process of these lesions in mice (See Abstract)

As an aside, it is noted that Mizuno et al also indicates that the position in the Advisory Action of May 1, 2002, that applicant needs to show the constitutive presence of cyclooxygenase-2 in liver for cyclooxygenase-2 inhibition to be counterindicated in the case of treatment of the claims, is not well taken. Mizuno shows that induced production of cyclooxygenase-2 can be protective--in such cases, inhibition of cyclooxygenase-2 would be detrimental.

The Contention by the PTO that the Applied Prior Art Combination Teaches that Selective Inhibitors of Cyclooxygenase-2 Are Known For Treating Liver Diseases is Overgeneralization and Overstatement

Gregory et al is relied on for the purposes of the rejection as teaching that selective inhibitors of cyclooxygenase-2 are known for treating liver disease.

This contention by the PTO constitutes overgeneralization. Gregory et al does not mention treating liver diseases generally. Gregory et al only mentions liver transplant rejection and primary biliary cirrhosis (a disease of unknown origin) but not any condition treated in the appealed claims.

This contention by the PTO is also submitted to be overstatement even if limited to treating liver transplant rejection and primary biliary cirrhosis. Gregory et al is submitted to be regarded as suspect even for the these two conditions by one skilled in the art. Gregory et al contains no data in respect to either of these conditions. The only working example in Gregory et al is directed to graft rejection, and it is prophetic. Moreover, Gregory et al lists as a condition for treating, inflammatory bowel disease (IBD). See column 5, line 63 of Gregory et al. It is submitted that Reuter et al discussed above contains data suggesting that administration of inhibitors of cyclooxygenase-2 are counterindicated for the treatment of IBD at least where ulcers are present. It is submitted that Reuter et al indicates that recitation in Gregory et al about utilities is unreliable and that reliance on Gregory et al is misplaced .

The Rejection Ignores that Consideration of the Art as a Whole Leads Away from the Invention

Further, consider that prostaglandins, compounds produced by action of cyclooxygenase-2, have been indicated as having been known at least since 1993 to protect

against LPS-induced liver injury by downregulation of the production of inflammatory cytokines. See statements and associated citations dating back to 1993 in Mokuno, Y. et al, Hepatology 36, 1464-372 (1999), copy enclosed with the response of June 5, 2002. This is submitted to indicate that administration of cyclooxygenase-2 inhibitors would deprive a patient of liver protecting prostaglandin and would be considered as counterindicated in the case of liver diseases.

Secondly, it is contended that the art as a whole also otherwise suggests that administration of cyclooxygenase-2 inhibitors would counterindicated in the case of liver disorders.

In regard to this contention, consider that the Arthritis Advisory Committee of the FDA concluded in 1982 that hepatotoxicity is class characteristic of NSAIDs (combination cyclooygenase-1/cyclooxygenase-2 inhibitors). See Zakim, D., et al, Hepatology A Textbook of Liver Disease, Volume II, Third Edition, W.B. Saunders, Philadelphia (1996), pages 9765 and 977, copy enclosed with the response of January 07, 2002.

The final rejection and advisory actions, in response to the position in the above paragraph contend that publications indicate the hepatotoxicity associated with NSAIDs, would not be considered by one skilled in the art as extending to selective inhibitors of cyclooxygenase-2 even though NSAIDSs are inhibitors of cyclooxygenase-2. The contention by the PTO is that publications indicate that the hepatoxicity is due to the cyclooxygenase-1 inhibition of NSAIDs.

The final rejection relied on Seibert, et al, CAPLUS Abstract, AN 1988:369098 for this position. Reliance on Seibert et al is submitted to be misplaced. The Seibert abstract is insufficient because it is dated 1998 whereas the instant patent application claims the benefit of U.S. Provisional Application No. 60/069,955 filed December 17, 1997 and thus the Seibert

abstract is dated too late to rely on. Moreover, it is submitted that the Seibert abstract is misinterpreted in the final rejection paper and that the toxicities referred to in the sentence relied on in the final action, constitute gastrointestinal toxicities and not all toxicities associated with NSAIDs or liver toxicities. See paragraph 11 of the declaration of the inventor, Dr. Dannenberg, submitted with the response of May 15, 2002. Moreover, the position in the office action is submitted to be defective even if the Seibert abstract is considered and misinterpreted, because it relies on a hypothesis, that is a tentative assumption without supporting proof or evidence. It is submitted that an unobviousness position cannot be based on a hypothesis because a hypothesis cannot provide the reasonable expectation of success which is required. It appears that the PTO is no longer is relying on the Seibert abstract in view of the above.

Instead the Advisory Action of June 21, 2002, relies on column 6, lines 39-49 of Gregory et al and column 1, lines 28-36 of Talley et al.

Column 6, lines 39-49 of Gregory et al is reproduced below:

> The term "cyclooxygenase-2 inhibitor" embraces compounds which selectively inhibit cyclooxygenase-2 over cyclooxygenase-1. Preferably, the compounds have a cyclooxygenase-2 IC_{50} of less than about 0.5 μM, and also have a selectivity ratio of cyclooxygenase-2 inhibition over cyclooxygenase-1 inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds have a cyclooxygenase-1 IC_{50} of greater than about 1 μM, and more preferably of greater than 20 μM. Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.

Column 1, lines 28-36 of Talley et al is reproduced below.

> Previous NSAIDs have been found to prevent the production of prostaglandins by inhibiting enzymes in the human arachidonic acid/prostaglandin pathway including the enzyme cyclooxygenase (COX). The recent discovery of an inducible enzyme associated with inflammation

> (named "cyclooxygenase-2) (COX-2)" or "prostaglandin G/H synthase II") provides a viable target of inhibition which more effectively reduces inflammation and produces fewer and less drastic side effects.

The recitation from Gregory et al is equivocal. The recitations from Gregory et al and Talley et al are both indefinite. Neither says the hepatotoxicity associated with NSAIDs is not present for selective inhibitors of cyclooxygenase-2. Those skilled in the art are submitted not to give the same weight to the recitations of Gregory et al and Talley et al as does the advisory action of June 21, 2002. Evidence of this is that he Physicians' Desk Reference (PDR) still indicates that selective inhibitors of cyclooxygenase-2 should not be utilized in the case of liver disorders. Consider that the PDR (2001) at page 2051 states:

> Use of VIOXX is not recommended in patients with moderate or severe hepatic insufficiency.

Consider that the PDR (2001) at page 2484, states:

> If clinical signs and symptoms consistent with liver disease develop... CELEBREX should be discontinued.

VIOXX and CELEBREX are selective inhibitors of cyclooxygenase-2. A copy of the pages 2051 and 2484 of the PDR was filed with the response of June 5, 2002. Consider that these PDR pages indicate that even currently, physicians do not prescribe selective inhibitors of cyclooxygenase-2 in the case of liver disorders. The recitations in Gregory et al and Talley et al about toxicities have not changed this. Moreover, the recitations in Gregory et al about use of selective inhibitors of cyclooxygenase-2 in the cases of liver transplant and primary biliary cirrhosis, have not changed this. Thus, Gregory et al has not been accorded the conclusions attributed to it in the office action by those skilled in the art, even though Gregory et al WO 97/29776, applied in the final action, having similar disclosure to U.S. Patent No, 6,172,096 in the respects relied on by the

PTO, was published in 1997. Thus the combination of Gregory et al and Talley et al, cannot be taken as refuting the 1982 conclusion of the Arthritis Advisory Committee that suggests that selective inhibitors of cyclooxygenase-2 would be counterindicated in the case of liver disorders.

No Analogy Has Been Shown Between Liver Transplant
or Primary Biliary Cirrhosis and the Disorders of the Claims

The final rejection is based on the contention that all inflammatory liver disorders including liver transplant and primary biliary cirrhosis (Gregory et al) and hepatitis (the claims) would be considered as a analogous, by those skilled in the art for treatment purposes. However, no publications or other evidence has been submitted by the PTO indicating this. Moreover, there is contrary evidence as of May/June 1997. In this regard, See Anderson, F. H. et al, Can. J. Gastroenterol. 11, No. 4, 294-297 (May/June 1997), copy enclosed with the reponse of June 5, 2002, which presents data that the NSAID ketoprofen in use in a combination of ketoprofen and interferon does not improve interferon-resistant hepatitis C. Moreover, this finding is confirmed by Zanski, J.-P, et al, Hepatology 27, 862-867 (1998), copy enclosed with the response of June 5, 2002, which presents data showing the NSAID tenoxicam is unable to increase response rate in patients with chronic hepatitis C treated by alpha interferon.

Thus, the only evidence of record suggests there is no analogy between the liver disorders disclosed in Gregory and the liver disorders as claimed, so far as treatment is concerned, even if Gregory is given credit for one skilled in the art accepting that it teaches useful treatment of liver transplant rejection and primary biliary cirrhosis (which appllicant contends should not be the case).

The Law and Its Application Here

Applicant bears the burden of coming forward with evidence or argument in response to any *prima facie* case. After applicant meets this burden, patentability is determined on the totality of the record, by preponderance of evidence, with due consideration to persuasiveness of argument. In re Oetiker, 24 USPQ 2d 1443 (Fed. Cir. 1992).

It is submitted that any *prima facie* case of prior art indicating that selective inhibitors of cyclooxygenase-2 are generally useful for treating inflammatory disease is rebutted by Reuter, G.K., et al and Mizuno, H., et al, discussed above.

It is submitted that no *prima facie* case has been established for selective inhibitors of cyclooxygenase-2 being useful to treat a class of liver disorders embracing those claimed. Analogy would have to be relied on for a *prima facie* case in respect to liver disorders. No evidence of analogy has been set forth in any office or advisory action, Contrary evidence is submitted to be provided by Anderson et al (confirmed by Zanski et al) discussed above.

Teaching or leading away is the very essence of unobviousness and compels a finding of patentability and overcomes any *prima facie* case. In re Malagari, 182 U.S.P.Q. 549 (C.C.P.A. 1974) and In re Buehler 185 U.S.P.Q. 781 (C.C.P.A. 1975). Here teaching away has been established by Mokuno et al, Zakim, PDR (2001) pages 2051 and 2484 and Anderson et al (confirmed by Zanski et al), discussed above.

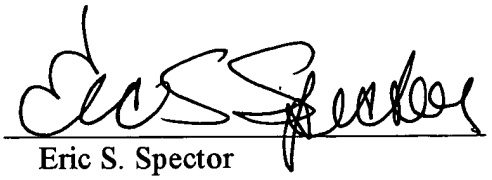
A reasonable expectation of success is required to be provided by the applied prior art combination,. In re O'Farrell, 7 U.S.P.Q. 2D 1673 (Fed. Cir. 1988). It is submitted that this is not present because of Mokuno et al, Zakim et al, PDR (2001) pages 2051 and 2084 and Anderson et al (confirmed by Zanski), discussed above.

Request

It is requested that the decision finally rejecting Claims 3-5 and 17 be reversed.

Respectfully submitted,

JONES, TULLAR & COOPER, P.C.

By: 

Eric S. Spector
Reg. No. 22,495

JONES, TULLAR & COOPER, P.C.
P.O. Box 2266 Eads Station
Arlington, Virginia 22202
703-415-1500

Case: CRF D-2165

Date: July 8, 2002

Appendix A

Appealed Claims (3-5 and 17)

3 (Amended). A method of treating a patient affected with liver disease selected from the group consisting of chronic viral hepatitis B, chronic hepatitis C, alcoholic liver injury and nonalcoholic steatohepatitis, comprising administering to said patient a cyclooxygenase-2 inhibiting amount of a selective inhibitor of cyclooxygenase-2.

4. The method of Claim 3, wherein the selective inhibitor of cyclooxygenase-2 is 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzensulfonamide.

5. The method of Claim 3, wherein the selective inhibitor of cyclooxygenase-2 is 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

17. (Amended) The method of Claim 3 wherein the selective inhibitor of cyclooxygenase-2 directly inhibits the enzyme cyclooxygenase-2 and also inhibits the synthesis of cyclooxygenase-2 protein and contains phenyl group with two or more substituents selected from the group consisting of hydroxy and C_{1-4}-alkoxy on the phenyl group.

Appendix B

Claims Withdrawn from Consideration

7. (Amended) A method of treating a patient with a virus-caused liver disease selected from the group consisting of chronic viral hepatitis B and chronic viral hepatitis C comprising administering to said patient a cyclooxygenase-2 inhibiting amount of selective inhibitor of cyclooxygenase-2 and therapeutic amount(s) of anti-viral drug(s).

9. (Amended) The method of Claim 7, wherein the selective inhibitor of cyclooxygenase-2 is 4-[5-(4-chlorophenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

10. (Amended) The method of Claim 7 wherein the selective inhibitor of cyclooxygenase-2 is 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide.

11. (Amended) The method of Claim 7 wherein the selective inhibitor of cyclooxygenase-2 directly inhibits the enzyme cyclooxygenase-2 and also inhibits the synthesis of cyclooxygenase-2 protein and contains phenyl group with two or more substituents selected from the group consisting of hydroxy and C_{1-4}-alkoxy on the phenyl group.